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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,750	05/16/2001	Madhavan Nampoothiri K.	32301WD1181	8888

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EXAMINER
STEADMAN, DAVID J

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,750	NAMPOOTHIRI K. ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/855,750* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

Claims 1-24 are pending in the application.

Applicants' election with traverse of Group I, claims 1-12, 23, and 24 in Paper No. 10, filed 07/22/02 is acknowledged.

It is noted that applicants state at page 1 of Paper No. 10 that the instant application is part of a series of applications associated with US Patent Application No. 09/954,197 and that papers received by applicants from the Office indicate these applications have been channeled to Art Unit 1646, asserted by applicants to be the enzyme technology art unit. Applicants note the examiner may consider consolidating this application with those in Art Unit 1646 for examination. The elected claims of the instant application are drawn to polynucleotides encoding a polypeptide having acyl-CoA synthase enzymatic activity. Art Unit 1652 primarily examines applications with claims drawn to enzymes, while Art Unit 1646 primarily examines applications with claims drawn to receptors, cytokines, and recombinant hormones. Therefore, it would appear the instant application is better suited for examination in Art Unit 1652.

Election/Restrictions

1. Applicants traverse the restriction requirement on the grounds that a search for all pending claims would not result in a burden on the examiner. Applicants argue a search for the claims of Group I will yield relevant art for the claims of Groups II and III and therefore, the search for the claims of Groups I-III would not be burdensome. Applicants' argument is not found persuasive. MPEP 803 states "[t]here are two criteria for a proper requirement for restriction between patentably distinct inventions", those criteria being: 1) the inventions must be independent or distinct and 2) there must be a burden on the examiner. The inventions were clearly demonstrated to be independent and distinct by the examiner in the restriction requirement of Paper No. 9 (see paragraphs 2-4 of Paper No. 9). Also, a search of each Group would require independent considerations that would require the examiner to focus on different features and entail differently structured word searches for both patent and non-patent literature for each

of the three inventions. The inventions of Groups II and III require a search for methods of producing L-amino acids using bacteria comprising genes in addition to the fadD15 gene of Group I. Therefore, a search for the claims of Group I would not be co-extensive with the claims of Groups II and III, and a search for the claims of Groups I-III would result in a burdensome search on the examiner. Therefore, each of the inventions of Groups I-III are independent and distinct and require a separate search.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Specification/Informalities

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "The FadD15 Gene of *Corynebacterium glutamicum*, Encoding An Acyl-CoA Synthase Polypeptide". See MPEP § 606.01.

Claim Objections

3. Claims 7, 10, and 12 are objected to for the use of improper sequence identifiers. It is suggested that applicants replace the term "SEQ ID No." with "SEQ ID NO:". See MPEP 2422 and 37 CFR 1.821 regarding identification of sequences in the claims and specification.

4. Claims 7, 10, 23, 24 are objected to because of the following informalities: the terms "polynucleotides of a) or b)" in claim 7 part c), "replication, and comprises" in line 2 of claim 10, "a polynucleotide sequences" in line 1 of claim 23 and lines 1 and 2 of claim 24, and "DNA of genes" in line 3 of claim 23 are grammatically incorrect and should be replaced with, for example, "polynucleotide of a) or b)", "replication comprises", "a polynucleotide sequence" or "polynucleotide sequences", and "DNA or genes", respectively. Appropriate correction is required.

5. Claim 23 is objected to in the recitation of "polymer chain reaction" in line 4. In the interest of clarity, it is suggested that the term be replaced with, for example, "polymerase chain reaction".

6. Claim 24 is objected to in the recitation of "isolate cDNA or genes". In the interest of clarity, it is suggested that the term be replaced with, for example, "hybridize to cDNA or genes".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1-12, 23, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 1-6 are indefinite in the recitation of "genetically modified coryneform bacterium". It is unclear from the claims as to whether the intended genetic modification results in amplification of the fadD15 gene or if the intended genetic modification has some other effect. It is suggested that applicants clarify the meaning of the claims.

9. Claims 1 (claims 2, 4, and 6 dependent therefrom), 3, and 5 are indefinite in the recitation of "fadD15 gene". It is noted the specification provides a description of "fadD15 gene" at page 3 as "the fadD15 gene... ...is SEQ ID NO 1 and related sequences". It remains unclear from this definition as to the scope of genes encompassed by this definition. It is suggested that applicants identify the "fadD15 gene" by a sequence identifier, e.g., SEQ ID NO:1.

10. Claim 2 recites the limitation "the starting bacterium" in line 2. There is insufficient antecedent basis for this limitation in the claim.

11. Claim 4 recites the limitations "the reading frame" in line 5, "the promoter" in line 5, "the regulation region" in line 6, "the ribosome binding site" in line 7, "the structural gene" in lines 8 and 9, "the corresponding mRNA" in line 10, and "the proteins expressed" in line 11. There is insufficient antecedent basis for these limitations in the claim.

12. Claim 4 is indefinite in the recitation of "the proteins expressed" as it is unclear from claim 4 or the claims from which claim 4 depends as to the proteins that are expressed. From the claims, the examiner can find reference to only a single expressed protein, i.e., acyl-CoA synthase. It is suggested that applicants clarify the meaning of the claim.

13. Claim 4 is confusing as the claim recites genetic modifications that do not result in gene amplification. Claim 4 depends from claim 3, which is limited to a coryneform bacterium with an amplified fadD15 gene, however, some of the recited modifications, e.g., prolonging the life of the corresponding mRNA, do not result in gene amplification. It is suggested that applicants clarify the meaning of the claim.

14. Claim 5 recites the limitations "the strain" in line 1 and "the nucleotide sequence" in line 4. There is insufficient antecedent basis for these limitations in the claim.

15. Claim 6 is indefinite in the recitation of "corresponds genotypically". The examiner can find no description of this term in the claims or the specification and the meaning of this term is unclear. It is suggested that applicants clarify the meaning of the term "corresponds genotypically".

16. Claim 7 (claims 8-12 dependent therefrom) is unclear in the recitation of "a polynucleotide... ...which codes for a polypeptide which comprises the amino acid sequence of SEQ ID No. 2, or consists of this" in part a). It is suggested that applicants clarify the meaning of the term "consists of this" as it is unclear as to applicants' intended meaning.

17. Claim 10 (claims 11 and 12 dependent therefrom) is unclear in the recitation of "the context of the degeneration of the genetic code" in part ii). It is suggested that applicants clarify the meaning of the claim. It is suggested that, for example, claim 10 part ii) be replaced with "a degenerate variant of the nucleotide sequence of i), or".

18. Claim 10 (claims 11 and 12 dependent therefrom) is indefinite in the recitation of "hybridizes" in part iii) as this term is unclear absent a statement of the conditions under which the hybridization reaction is preformed. Nucleic acids that will hybridize under some hybridization conditions will not necessarily hybridize under different conditions. It is noted that a vague definition of hybridization

conditions is provided at pages 6 and 7 of the instant specification. However, no specific hybridization conditions are provided.

19. Claim 10 (claims 11 and 12 dependent therefrom) is indefinite in the recitation of "complementary". Neither the specification nor the claims provides a definition of the term "complementary" and it is unclear whether the complementary strand is a partial or complete complement. It is suggested that applicants clarify their meaning of the term "complementary" with, for example, "completely complementary".

20. Claim 11 is indefinite in the recitation of "mutations of neutral function... ...which lead to homologous amino acids". It is unclear from the claims and the specification as to which possible "mutations of neutral function" may lead to homologous amino acids. As such, it is unclear as to applicants' intended mutations. It is suggested that applicants clarify the meaning of the term.

21. Claim 24 is indefinite in the recitation of "high homology with the sequence of the fadD15 gene". The term "high homology" is a relative term and it is unclear from the claims as to the degree of homology to which applicants' intend to be "high homology". It is noted that applicants have provided a description of the term "homologous" and "homologous protein" at page 5 of the specification. Based on this definition, the examiner has interpreted the term "high homology" as meaning "at least 90 % homology". If the examiner's interpretation of these claims is incorrect, applicant should so state and clarify the record.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

22. Claims 1-5, 7-11, 23, and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 are drawn to a genus of genetically modified coryneform bacteria having an amplified fadD15 gene from any source. Claim 7 parts a) to d) are drawn to a genus of polynucleotides that are 70 % identical to a nucleic acid encoding SEQ ID NO:2, a genus of polynucleotides encoding polypeptides that are 70 % identical to SEQ ID NO:2, a genus of complements thereof, and a genus of polynucleotides comprising at least 15 nucleotides of the polynucleotide of a), b), or c) of claim 7 that have not been fully described in the specification. Claim 10 part (iii) is drawn to a sequence that hybridizes to parts (i) or (ii) of claim 10 and having any function. Claim 11 is drawn to a genus of polynucleotides of claim 10 part i) having mutations of neutral function which lead to homologous amino acids that have not been fully described in the specification. Claims 23 and 24 are drawn to a genus of primers comprising a polynucleotide of claim 7 or parts thereof that can produce DNA or all genes coding for acyl-CoA synthase by PCR or a genus of hybridization probes comprising a polynucleotide of claim 7 that can hybridize to cDNA or genes having a high homology with the sequence of any fadD15 gene that have not been fully described in the specification.

Regarding claims 1-6, 23, and 24, the specification teaches only a single representative species of such genetically modified coryneform bacteria, i.e., a coryneform bacterium transformed with an expression vector comprising SEQ ID NO:1, two representative species of PCR primers, i.e., SEQ ID NOs:3 and 4, and the specification teaches only a single representative species of such hybridization probes, i.e., the polynucleotide of SEQ ID NO:1. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a genetically modified coryneform bacterium with an amplified fadD15 gene, a primer comprising a polynucleotide of claim 7 or parts thereof that can produce DNA or genes coding for acyl-CoA synthase by PCR, or a hybridization probe comprising a polynucleotide of claim 7 that can hybridize to cDNA or genes having a high homology with the sequence of any fadD15 gene.

Regarding claims 7 (claims 8 and 9 dependent therefrom) and 11, the specification does not contain any disclosure of the function of all polynucleotide sequences comprising at least 15 nucleotides of the polynucleotide of a), b), or c) of claim 7 and the specification does not contain any disclosure of the function of all polynucleotides of claim 10 with mutations of neutral function that lead to homologous amino acids. The genus of claimed polynucleotides is a large variable genus with the potentiality of encoding many different proteins. Therefore, many functionally unrelated polynucleotides are encompassed within the scope of these claims, including partial polynucleotide sequences. The specification discloses only a single species of the claimed genus, i.e., SEQ ID NO:1, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Therefore, because the genera of genetically modified coryneform bacteria, polynucleotides, primers, and hybridization probes have not been fully described according to 35 USC 112, first paragraph, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

23. Claims 1-5, 7-11, 23, and 24 are rejected under 35 U.S.C. 112, first paragraph, because the scope of the claims is not commensurate with the enablement provided in the specification. The specification provides enablement for a polynucleotide encoding the polypeptide of SEQ ID NO:2, the polynucleotide of SEQ ID NO:1, and a coryneform bacterium transformed with an expression vector comprising SEQ ID NO:1. However, the specification does not reasonably provide enablement for all coryneform bacteria or the coryneform bacteria of claim 2 having any genetic modification resulting in amplification of a fadD15 gene from any source (claims 1 and 2), and optionally wherein the amplification is due to overexpression by any genetic modification (claim 3) or the modifications of claim 4, or optionally wherein the genetic modification is transformation of a plasmid comprising a nucleotide sequence of a fadD15 gene from any source (claim 5), all coryneform bacteria polynucleotides comprising: polynucleotides that are 70 % identical a polynucleotide encoding SEQ ID NO:2, polynucleotides encoding polypeptides that are 70 % identical to SEQ ID NO:2, complements thereof,

and polynucleotides having at least 15 successive nucleotides of the polynucleotides of a), b), or c) of claim 7, all polynucleotides that hybridize with the sequence complementary to (i) or (ii) of claim 10, all polynucleotides of claim 10 part i) having mutations of neutral function (claim 11), all primers comprising a polynucleotide of claim 7 or parts thereof that can produce all genes coding for acyl-CoA synthase by PCR (claim 23), or a hybridization probe comprising a polynucleotide of claim 7 that can hybridize to DNA having a high homology with the sequence of any fadD15 gene (claim 24). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-5, 7 (claims 8 and 9 dependent therefrom), 10, 11, 23, and 24 are so broad as to encompass any genetically modified coryneform bacterium, polynucleotide, primer, or hybridization probe as described above. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of genetically modified coryneform bacteria, polynucleotides, primers, and hybridization probes broadly encompassed by the claims.

Regarding the genetically modified coryneform bacterium, applicants have provided no guidance or working examples, other than the disclosure of transforming a coryneform bacterium with an expression vector comprising SEQ ID NO:1, for genetically modifying a coryneform bacterium for amplification of any fadD15 gene. One of skill in the art would recognize that without guidance or working examples, genetic modifications to an organism with an expectation of obtaining amplification of a specific gene are highly unpredictable. Further, applicants have provided no guidance as to the nucleotide sequence or methods of isolation of fadD15 genes from organisms besides Corynebacterium

glutamicum and neither the specification nor the prior art provides guidance as to the predictability that the sequences of other fadD15 can be isolated based on the structural information of SEQ ID NO:1 provided in the specification. Therefore, an undue amount of experimentation would be required to isolate all genetically modified coryneform bacteria as described above.

Regarding the polynucleotides, primers, and probes, the nucleic acid sequence of a polynucleotide determines the encoded protein's structural and functional properties, predictability of which changes can be tolerated in an encoded protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a polynucleotide encoding the polypeptide of SEQ ID NO:2, the polynucleotide of SEQ ID NO:1, and a coryneform bacterium transformed with an expression vector comprising SEQ ID NO:1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within an encoded protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. It is known in the prior art that even a minor number of amino acid substitutions can result in a polypeptide with altered function. For example, Broun et al. (Science 282:1315-1317) teach that as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase (page 1315, abstract). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all genetically modified coryneform bacteria, polynucleotides, primers, and hybridization probes as described above because the specification does not establish: (A) methods of modifying a coryneform bacterium by

methods other than transformation as described above with an expectation of obtaining the desired result; (B) nucleotide sequences or methods of isolation of fadD15 genes other than SEQ ID NO:1; (C) regions of the nucleic acid structure of SEQ ID NO:1 that may be modified without affecting the encoded polypeptide activity; (D) the general tolerance of the polypeptide encoded by SEQ ID NO:1 to modification and extent of such tolerance; (E) a rational and predictable scheme for modifying any residues of SEQ ID NO:1 with an expectation of obtaining an expressed polypeptide with the desired biological function; (F) primers and probes as encompassed by the claims that can produce or hybridize to any gene encoding an acyl-CoA synthase or having high homology with any fadD15 gene; and (G) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any genetically modified coryneform bacteria, polynucleotides, primers, and hybridization probes as described above. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re* Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re* Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

24. All claims are rejected. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 2:00 pm and from 3:30 pm to 5:30 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600